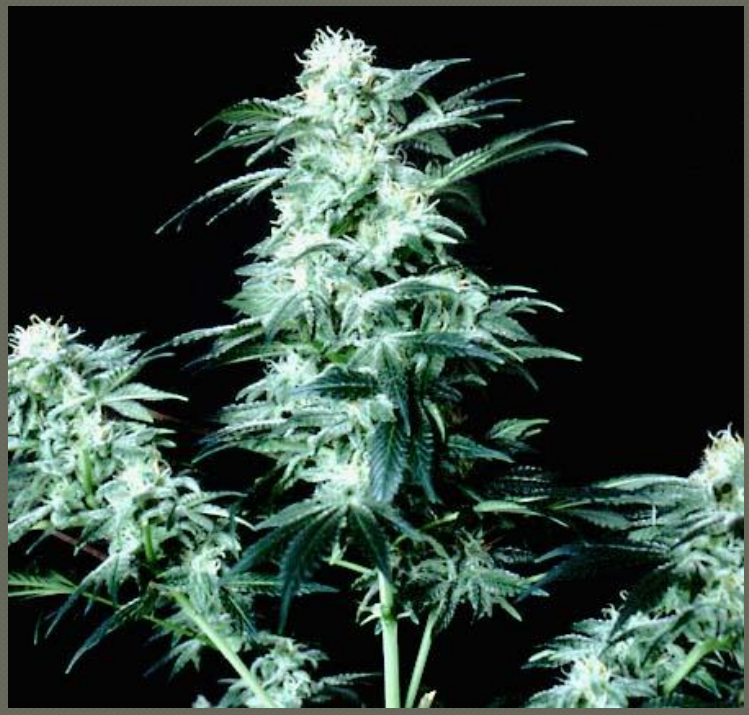
Marijuana

- Cannabis sativa
- Tetrahydrocannabinol (THC)



Early History

- India
  - Bhang--tea
  - Ganja—leaves, flowers
  - Charas--hashish/hash

Cannabis Preparations

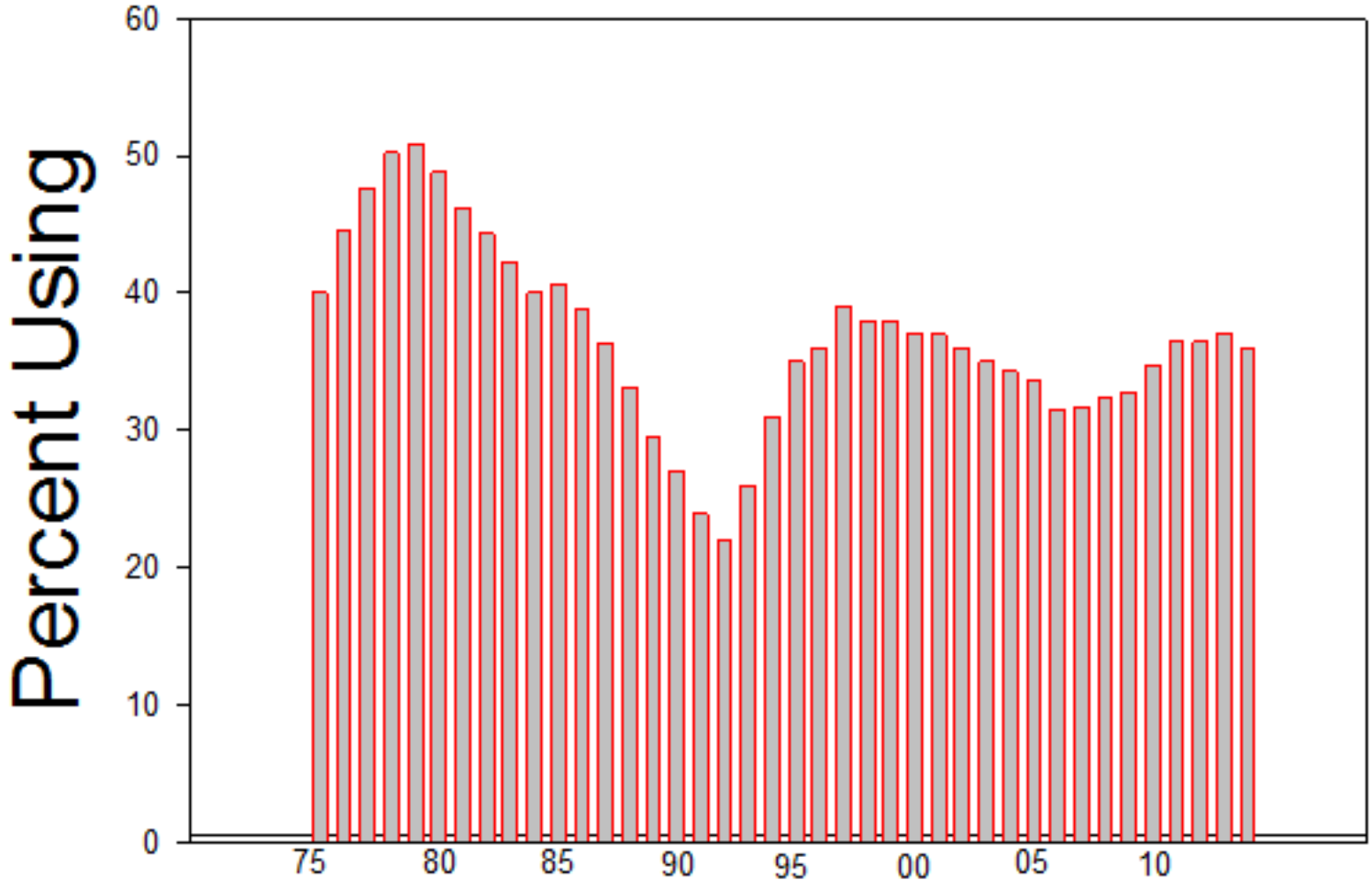
Name	Part of Plant	THC
Marijuana	Leaves, stems	4-6 %
	Recent strains; flower heads	8-12%
Hashish	Cannabis resin	10-15 %
Cannabis/ Hash Oil	Resin concentrate (alcohol extract)	20-60 %
BHO	Resin concentrate (butane extract)	80%

Middle History

- Europe & America's: Hemp
- The Hashish Club
- 1937 Marijuana Tax Act

Henry Anslinger

Percent High School Seniors reporting Marijuana use during their Senior year



Marijuana in the USA ()

- Munsey, 2010
  - 81% approve of medical use of marijuana
  - 72% say that marijuana possession should lead to fine, not jail
  - 44% support outright legalization
  - 47% say that they have tried marijuana at least once
- Gallup, 2015: 52% support legalization

Marijuana Use in the USA

- Largest cash crop in USA at >$35 billion/year
- Enforcement of marijuana laws costs >$7 billion/year
- Decriminalized in many states, but remains illegal; Schedule I in federal system

Marijuana Use in the USA

Legal recreational marijuana passed in Colorado and Washington Nov 2012

Marijuana in WA & CO

- WA—sales began July, 2014

- CO (January 1, 2014)
  - Sales limited to adults (> 21 yrs)
  - 160 licensed vendors (50 in Denver)
  - Residents may purchase 1 oz (28 g)
  - Fodor's guide to pot tourism: Non-residents only ¼ oz (7 g)
  - Prohibited in public places; some cities (e.g., Vail ski resort)
  - More than $1 million brought in on the first day in business!

Issues re Legal Marijuana

- Banking
  - Because Marijuana remains Schedule I banks face possible charges for handling $$
  - Cash business invites crime

Issues re Legal Marijuana

- Marijuana edibles
  - use by children

Issues re Legal Marijuana

.

- Illegal exports of Colorado marijuana have been seized in more than 40 states

Marijuana and the Brain

- Discovery of THC receptors

Marijuana and the Brain

- Discovery of THC receptors (CB1)
- Anandamide : The brain's own marijuana (from Ananda: Hindu word for bliss)

Pharmacokinetics of THC

- Rapid absorption in lung
- 2-5 hr duration of action
- Erratic absorption after oral admin.

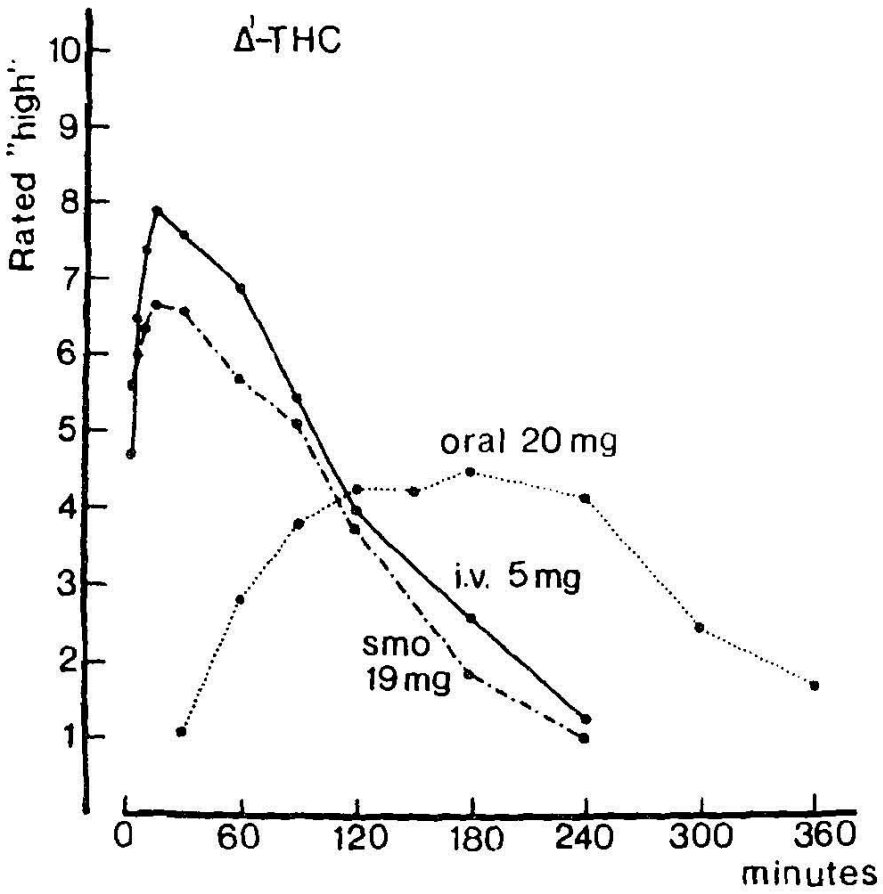


Figure 2.5. Time course of the subjective "high" after administering THC by different routes. Smoking gives as rapid an effect as an intravenous injection, whereas taking the drug by mouth produces a delayed and prolonged high. The subjective experience somewhat outlasts the presence of THC in blood (see Fig. 2.5) because THC persists longer in the brain. (From Agurell et al., 1986.)

Pharmacokinetics of THC

- Rapid absorption in lung
- 2-5 hr duration of action
- Erratic absorption after oral admin.
- Great persistence in tissue: 30 days after a single dose

- Detection in urine 10-14 days after a single dose; up to 24 days after chronic use (Lowe et al. (2009)

Acute Marijuana Effects: Physiological Actions

- Increase Heart Rate
- Lower Blood Pressure
- Dilation of blood vessels in the eye
- Dry mouth
- Increased appetite
- High doses are sedating

Medical Use of Marijuana?

- Glaucoma—not effective
- Nausea: adjunct to chemotherapy
- Cachexia: wasting in AIDS and cancer
- Multiple sclerosis: reduce spasticity
- Pain (particularly multiple sclerosis and neuropathic pain)

Medical Use of Marijuana

- Marinol (synthetic THC)—oral use only—problems for use with nausea
- Sativex—THC extract droplets taken in spray form—approved in Europe; Phase III in US

States with Medical Marijuana Laws

- California
- Oregon
- Washington
- Alaska
- Vermont
- Rhode Island
- Michigan
- Arizona
- Delaware
- Illinois
- New York
- Maryland
- Nevada
- Colorado
- Maine
- Hawaii
- New Jersey
- New Mexico
- Montana
- Connecticut
- DC
- Minnesota
- New Hampshire

FDA 2007 review: “smoked marijuana has no currently accepted medical use in the US and is not approved for medical treatment”

Psychological Effects of THC

- Subjective effects--variable
  - Tingling sensations in body and head (buzz)
  - Euphoria/sharpened humor/relaxation
- Acute changes in time perception, etc.
- Acute impairment of Short Term Memory

Psychological Effects of THC

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  - Tingling sensations in body and head (buzz)
  - Euphoria/sharpened humor/relaxation
- Acute changes in time perception, etc.
- Acute impairment of Short Term Memory
- Weil's study and Reverse Tolerance

- Impairment of motor skills/driving performance

Adverse Effects of Marijuana: Myth and Reality

- Acute impairment of complex motor skills
  - 10% highway fatalities driver THC positive
  - Only 30% under THC fail field sobriety test
  - Huestis (2014) THC intoxication increases crash risk twofold (about level of 0.05 alcohol)
    - Attentional problems
    - Slower decision making
    - Impaired peripheral vision

DUI in Colorado

- New DUI law is in effect in Colorado which sets a legal limit for the amount of active THC in your system while driving: 5 ngs per ml of blood.
- Controversial because data on impairment at this dose is not clear—THC is absorbed in fatty tissue and brain and blood levels begin to drop while impairment is still peaking. 5 ng/ml is very high and has been criticized as license to drive stoned (Dupont, 2014)

Adverse Effects of Marijuana: Myth and Reality

- Acute impairment of STM
- Acute impairment of complex motor skills
  - 10% highway fatalities driver THC positive
  - Only 30% under THC fail field sobriety test
  - Huestis (2014) THC intoxication increases crash risk twofold (about level of 0.05 alcohol)
- Increased heart rate
- Paranoia/Anxiety/panic
- Pregnancy?

Adverse Effects Attributed to Marijuana Use (Iversen, 2008)

Impaired memory	6.1%
Paranoia	5.6%
Amotivation	4.8%
Respiratory	4.2%
Anxiety/panic	1.8%
Total reporting problems	21.0%

Adverse Effects of Marijuana: Chronic Effects

- Lung damage

Carcinogens in smoke

- **Marijuana**
  - Vinyl Chloride 5 ng
  - D-M nitrosamine 75 ng
  - M ethylnitrosamine 27 ng
  - Benz-anthracene 75 ng
  - Benz-pyrene 31 ng
- **Tobacco**
  - Vinyl Chloride 12 ng
  - D-M nitrosamine 84 ng
  - M ethylnitrosamine 30 ng
  - Benz-anthracene 43 ng
  - Benz-pyrene 21 ng

Adverse Effects of Marijuana: Chronic Effects

- Lung damage
- Pletcher et al. JAMA (2012) large scale study
- Moderate pot smoking (2-3 times per week) did not impair lung function; some decline noted in heavier users—less lung toxicity than tobacco

Dependence on Marijuana

- Tolerance
- Withdrawal syndrome (Budney, 2010)
  - Irritability, mood changes
  - Sleep disturbances
  - Loss of appetite, nausea
  - Craving
  -
- 5% heavy users: 15+ joints per day; "more or less permanently stoned" House of Lords Cannabis report (2000)

Dependence on Marijuana

- DSM diagnosis requires neither tolerance nor physical withdrawal
- About 10% of those who use marijuana meet DSM-IV dependence criteria (NIDA, 2008)
  - Heroin-45%
  - Tobacco-32%
  - Cocaine-20%
  - Alcohol-15%
  - Marijuana—10%

Adverse Effects of Marijuana: Chronic Effects

- Lung damage
- Dependence
- Cognitive deficits?

Cognitive deficits

- Deficits on tests of memory, learning and processing speed persist 2-7 days after last use in chronic marijuana users (Iversen, 2008), but return to control levels after this
- Attentional deficits may be more persistent (Solowij, 1998; Iversen, 2008).

Adverse Effects of Marijuana: Chronic Effects

- Lung damage-Bronchitis, Lung cancer?
- Dependence
- Cognitive deficits?
- Amotivational syndrome?
  - No experimental support for this

Synthetic Cannabinoids: Spice/K2

- Non-psychoactive vegetable material with synthetic CB-1 receptor agonists sprayed on (e.g., HU-210, JWH-018)
- Effective when smoked; some effective orally
- Effects are THC-like but variable and largely unknown
- Sold on internet and in head shops

Synthetic Cannabinoids: Spice/K2

- DEA conducted over 400 analyses
- All were laced with a synthetic cannabinoid
- High variability between products, even the same label: Constituents and components change within product label and batch to batch

Synthetic Cannabinoids: Spice/K2

- Effects are THC like but variable and largely unknown
- ER poison center calls involving synthetic cannabinoid OD:
  - 2009—112
  - 2010—2,915
  - 2011—6,968
  - 2012—5,230
  - 2013—2,936

Synthetic Cannabinoids: Spice/K2

- 11.3% of high school seniors had used spice during the past year (2012)
- Synthetic Drug Abuse Prevention Act July, 2012 bans several cannabinoids:

  CP-47,496, JWH-018, -019, -073, - 122, -398; AM-678, -2201, Sr-19, RCS-4

2015 update: New cannabinoids on emergency list

- PB-22—QUPIC
- 5-F-PB-22
- AB-FUBINACA
- ADB-PINACA

- Dozens more not covered!

2015 update: New cathinones on emergency list

- 4-MePPP
- Alpha-PVP
- Butylone
- Pentedrone
- Pentylone
- 4-FMC
- 3-FMC
- Alpha BMP

Synthetic Cannabinoids (Spice)

- Highly potent full CB1 receptor agonists; as much as 1000 times more potent than THC (a relatively weak agonist)
- Few have been tested in humans
- Analysis of web reports suggests toxic effects more likely than with marijuana (Bush, 2014)

Synthetic Cannabinoids (Spice)

- Panic attacks; Psychotic reactions
- Nausea & vomiting
- Tachycardia; hypertension (Numerous reported OD deaths

Hallucinogens

- Serotonergic
- Methylated Amphetamines
- Anti-cholinergic
- Anesthetic
- Kappa-Salvia

MDMA tablets

Serotonergic Hallucinogens

- Lysergic acid diethylamide (LSD, Acid)

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- Psilocybin-Psilocybe mushrooms-Shrooms

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- Mescaline-Peyote cactus, San Pedro cactus

Peyote cactus-mescaline

Religious Use of Hallucinogens

- Right to peyote ritual is protected for Native Americans (affirmed in 2009 ruling in Utah)

Serotonergic Hallucinogens

- Lysergic acid diethylamide (LSD, Acid)
- Psilocybin-Psilocybe mushrooms-Shrooms
- Mescaline-Peyote, San Pedro cacti
- Dimethyltryptamine (DMT); Harmaline-Ayahuasca, Yage'----The Spirit Molecule

Religious Use of Hallucinogens

- Right to peyote ritual is protected for Native Americans (affirmed in 2009 ruling in Utah)
- Supreme Court approved religious use of ayahuasca tea (DMT/harmaline) for Brazilian religious group: Uniao do Vegetal in 2006

Serotonergic Hallucinogens

- Psilocybin-Psilocybe mushrooms
- Mescaline-Peyote, San Pedro cacti
- Dimethyltryptamine (DMT)– Ayahuasca
- Lysergic acid diethylamide (LSD, Acid)
- Phenethylamines (2C-B, 2C-I etc.)

Effects of LSD, 2C-I, psilocybin, etc…

- Serotonin 2a receptor (5-HT2a)
- Sympathomimetic
- Visual hallucinations

Visual Hallucinations

- Enhanced color perception
- Flickering of the visual field
- Perception of motion
- Synesthesia
- Form constants

Visual Hallucinations

- Enhanced color perception
- Flickering of the visual field
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- Form constants

Effects of LSD etc…

- Sympathomimetic
- Visual hallucinations
- Altered consciousness
- Spiritual/Mystical experiences
  - Griffiths et al. (2011) 94% rated psilocybin experience as among the 5 most significant spiritual event in their lives 1 year after experiment
- Tolerance (but no dependence)

Adverse Effects: Myth & Reality

- Birth defects/chromosome damage
  - Myth!
- Acute Psychotic Reactions (Bad Trips)
  - Fairly Common
- Use 7 times and legally insane
  - Myth!
- Residual Psychosis
  - Rare; not certainly related to LSD

Adverse Effects: Myth & Reality

- Flashbacks
  - Fairly common among heavy users
- For some people, flashbacks are constant
  - Rare, but true: hallucinogen persisting perception disorder
- Stored in spine?
  - Myth—Causes of flashbacks unclear

Serotonergic Hallucinogens

- Lysergic acid diethylamide (LSD, Acid)
- Psilocybin-Psilocybe mushrooms-Shrooms
- Mescaline-Peyote cactus
- Dimethyltryptamine (DMT); Harmaline-Ayahuasca, Yage'
- Synthetic phenethylamines (PEAs): 2C-B, 2C-I, (smiles, bees, nexus)

Phenethylamines

- PEAs are sold in head shops and on internet –some still legal
- Dose-effect functions of PEAs are largely unknown and recommended doses often guesswork
- Internet preparations of 2C-I and 2C-E led to numerous fatal overdoses last year

Synthetic Hallucinogens banned by July 2012 Synthetic Drug Abuse Prevention Act

- 2-(2,5-Dimethoxy-4-ethylphenyl)ethanamine (2C–E).
- "(21) 2-(2,5-Dimethoxy-4-methylphenyl)ethanamine (2C–D).
- "(22) 2-(4-Chloro-2,5-dimethoxyphenyl)ethanamine (2C–C).
- "(23) 2-(4-Iodo-2,5-dimethoxyphenyl)ethanamine (2C–I).
- "(24) 2-[4-(Ethylthio)-2,5-dimethoxyphenyl]ethanamine
- (2C–T–2).
- Dozens more PEAs remain legal

Methylated Amphetamines

- Are also PEAs
- Methylenedioxymethamphetamine (MDMA, Ecstasy, XTC, Molly)
- Methylenedioxyamphetamine (MDA)
- MDE (Eve)

MDMA tablets

History

- Patented by Merck in 1914
- Advocated by some as adjunct to psychotherapy (1970s-80s)
- Picked up the name "ecstasy" & became significant street drug (1980s)
- Schedule I drug (1986)
- Prototype "club drug" (1990s)

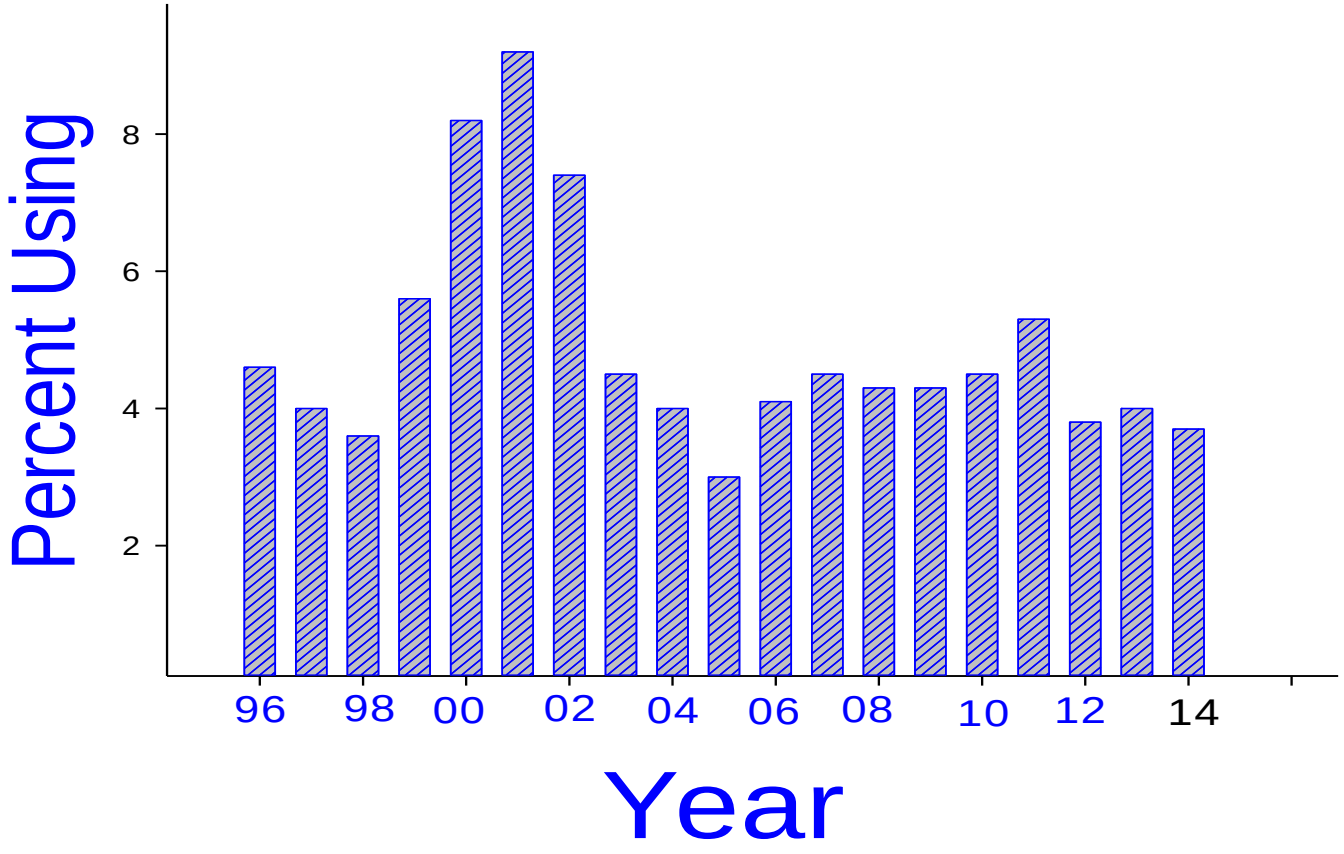
Ecstasy (MDMA): Psychological Effects

- Increased alertness, arousal, insomnia--stimulant effects
- Euphoria, increased emotional warmth
- Entactogen: Increased empathy and insight?
  - DeWit (2014; 2015) subjects on MDMA showed more sociality, empathy and more liking for others than those on Meth or placebo
- Hallucinogenic effects are largely absent

Ecstasy (MDMA): Physiological Effects

- Sympathomimetic
- Bruxism & Trismus—teeth grinding & jaw clenching (pacifiers)
- Dehydration/Overhydration
- Hyperthermia
- Tachycardia
- Collapse/Overdose death

Percent High School Seniors reporting MDMA use during their Senior year (Johnston, O'Malley, Bachman & Schulenberg, 2015)



Ecstasy and the brain

- MDMA increases release and blocks reuptake of serotonin
- MDMA also increases release of dopamine, and norepinephrine

LSD vs. Ecstasy

- Serotonergic hallucinogens chemical structures vary, but all are agonists of serotonin -2A receptors (5-HT2A)—pronounced visual hallucinations
- Methylated amphetamines (e.g.,MDMA—ecstasy) stimulate release and block reuptake of DA and serotonin—generally don't produce visual hallucinations

Ecstasy and the brain

- MDMA increases release and blocks reuptake of serotonin
- MDMA also increases release of dopamine, and norepinephrine
- Long term depletion of serotonin—damage to serotonin neurons in nonhumans

Are doses used in preclinical research too high?

- Although neurotoxic doses in non-humans (5-20 mg/kg twice or more/day for several days) are higher than typical human use, people often take several tablets at a time or throughout an night's binge and a tablet may contain up to 300 mg: 4-5 mg/kg in an average person.

What's in that pill?

- Molly v. Pills
- Piperazines: MCPP, TFMPP
  - Developed to treat worm infestations
  - Amphetamine-like stimulants
  - Now Schedule I
  - Often sold as "Molly"

http://www.ecstasydata.org

Ecstasy in humans

- Iversen (2008) review: Heavy users more depression, sleep disorders, memory problems than controls

Ecstasy in humans

- Iversen (2008) Heavy users more depression, sleep disorders, memory problems than controls
- What is the proper control group?
- Dauman et al. (2004) Heavy ecstasy users more depression than non-users, but not more than other drug users.
- De Sola et al. (2008) Memory deficits in MDMA users, but also in group matched for THC use that used no MDMA

Ecstasy in psychotherapy?

- Clinical trial for PTSD—Mithoefer (2011; 2013) better improvement w MDMA-aided psychotherapy

Medical uses of hallucinogens?

- Anxiety/depression in terminal patients (LSD, psilocybin)—research ongoing
- Addiction (psilocybin, ibogaine)—research ongoing
- Post-traumatic stress (MDMA)—research ongoing
- Depression (ketamine, psilocybin)--research ongoing

Anesthetic Hallucinogens

- Phencyclidine (PCP, Angel dust, Lovely)
- Ketamine (Special K)
- Methoxetamine (mexxie, roflcopter)

Anesthetic Hallucinogens

- Glutamate antagonists
- Euphoria, numbness, loss of motor coordination, blurred vision
- Nystagmus
- Distortions of body image, not visual hallucinations-in the K-hole
- High rate of psychotic episodes some long-term—model for schizophrenia?
- Ketamine as a rapid treatment for depression?

Naturally-Occurring Opiates

- Opium--from the poppy

Papaver somniferum

More than 90% of the world's opium is grown in Afghanistan

Naturally-Occurring Opiates

- Opium--from the poppy
- Morphine--from opium
- Codeine--from opium

Naturally-Occurring Opiates

- Opium--from the poppy
- Morphine--from opium
- Codeine--from opium
- Heroin--from morphine

Recent Wilmington Student Heroin Overdoses:

Jeffery Irby, 23
Co-captain UNCW sailing team

Renee Guinn, 21

Blaire Thompson, 20

Opiate Effects

- Pain relief--Analgesia
- Euphoria

Opiate Effects

- Mimic endorphins
  - enkephalin
  - Beta-endorphin
- Pain relief--Analgesia
- Euphoria

Naturally-Occurring Opiates

- Opium--from the poppy
- Morphine--from opium
- Codeine--from opium
- Heroin--from morphine

Synthetic Opiates

- methadone--Dolophine
- meperidine--Demerol
- propoxyphine—Darvon
  - Pulled from market Nov. 2010—heart rhythm abnormalities
- hydrocodone—Vicodin, Lorcet, Lortab
- oxycodone—Percodan, Oxycontin
- oxymorphone--Opana
- buprenorphine--Suboxone

Opiate Effects

- Analgesia/Euphoria
- Depression of HR, BP, Respiratory rate
- Decreased body temperature
- Pinpoint pupils
- Constipation
- Sexual disinterest--impotence
- Tolerance/Dependence

Opiate Withdrawal

- Runny nose/Sneezing/Tearing
- Pain
- Fever/Chills/Piloerection (goosebumps)
- Nausea and Diarrhea
- Spastic movements in legs and arms
- Spontaneous erection/orgasm
- Cross-dependence (and tolerance) between all opiate drugs (but not alcohol/depressants)

The Nature of Addiction

- Moral model (punishment/jail)
- Disease model (American)—12 Step (abstinence)
- Biological model (pharmacotherapy)
- Social-Learning/Sociocultural model (harm reduction/psychotherapy)

Biobehavioral model

- Biological factors
  - genetics/neurochemistry/withdrawal
- Psychological factors
  - comorbidity/stress/personality

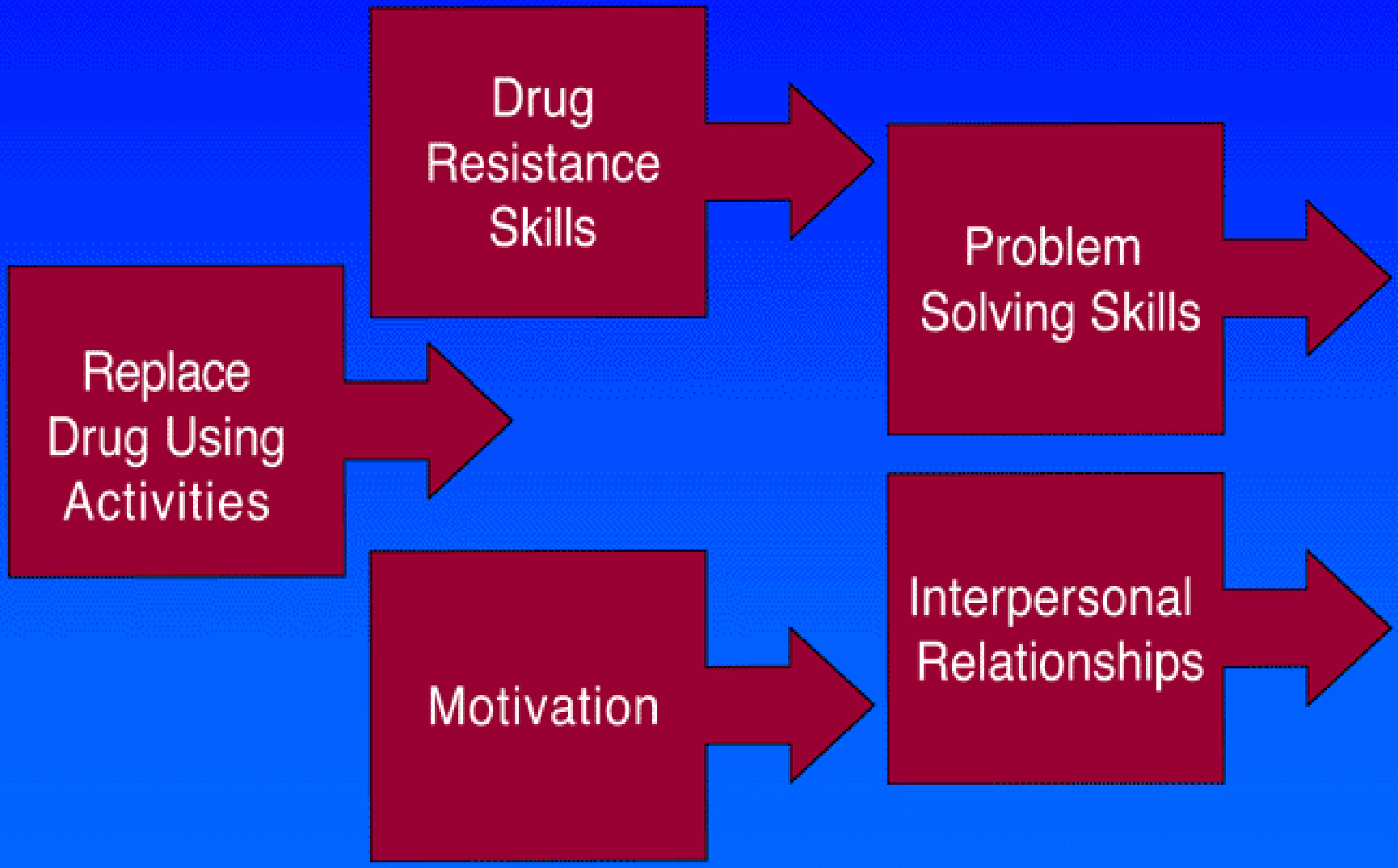
Biobehavioral model

- Biological factors
  - genetics/neurochemistry/withdrawal
- Psychological factors
  - comorbidity/stress/personality
- Social factors
  - culture/availability/peer and family/SES
  - Vietnam heroin epidemic

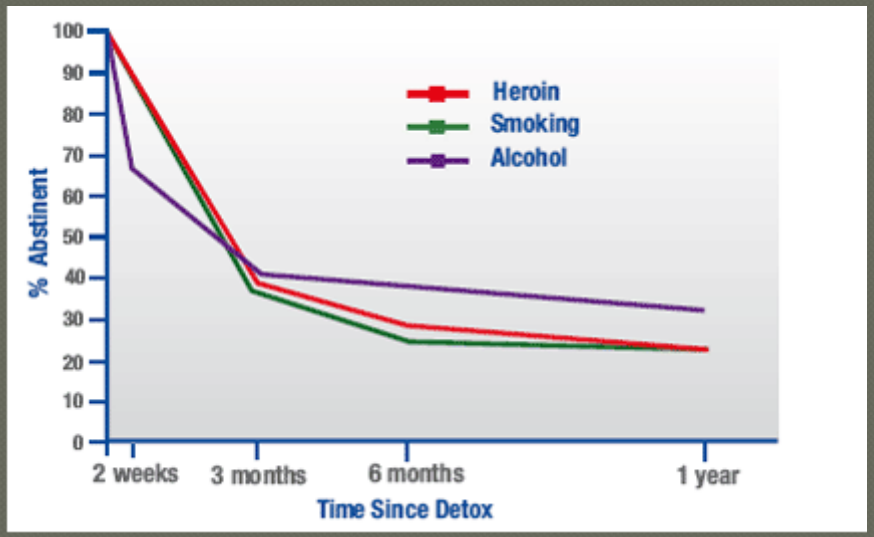
Treatment Modalities

- Outpatient
- Intensive Outpatient
- Short-term Inpatient

Counseling and Other Behavioral Therapies



Relapse Prevention



Treatment Modalities

- Outpatient
- Intensive Outpatient
- Short-term Inpatient
- Therapeutic Community
- Long-term follow-up: 12-step
- Pharmacotherapy

Pharmacotherapies

- Substitution therapy
- Anti-drug drug therapy

Substitution therapy

- Methadone

Substitution therapy

- Methadone
- Buprenorphine (Suboxone)
  - Combo of buprenorphine & naloxone
  - Effective sublingually, not injected
- Benzodiazepines
- Antidepressants and cocaine

Anti-drug drugs

- Antabuse (disulfiram)
- Revia (Trexan, naltrexone)